EXTRACELLULAR MATRIX MOLECULES AS REGULATORS OF ANGIOGENESIS

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Many cellular responses are dictated by the composition and organization of the extracellular microenvironment. The genesis of capillaries, for example, depends on interactions between growth factors and extracellular proteins. To understand specific mechanisms underlying the angiogenic process, we have studied the synthesis of extracellular matrix molecules by endothelial cells as they organize into cords and tubes, a process known as angiogenesis *in vitro*. Spontaneous morphogenesis of tubes under conventional culture conditions has been reported as an intrinsic characteristic of a variety of endothelial cells. We used endothelial cells derived from aorta and from capillaries and found that both large vessel, as well as microvascular endothelial cells, manifested the same pattern of changes in the synthesis of extracellular matrix proteins after they initiate the organization of cords and tubes. This biochemical profile included a significant increase in the levels of SPARC and type I collagen and a decrease in thrombospondin-1. Further studies suggested that these three molecules might regulate specific cellular functions during angiogenesis *in vivo*. Addition of SPARC to angiogenic cultures promotes changes in cell shape that might be required for the active migration of endothelial cells and further organization of cords. SPARC also stimulates the secretion of plasminogen activator inhibitor-1 and fibronectin and decreases the level of thrombospondin. The effect of SPARC on the expression of these proteins might result in a ratio of proteases to antiproteases that favors the angiogenic phenotype. Type I collagen has been observed in the lumen of endothelial cords, and we have suggested that type I collagen fibrils could serve as tracks to guide the migration of endothelial cells and the stabilization of tubes. Finally, we have observed that anti-thrombospondin antibodies increase cord formation by 33-50%. These results imply that thrombospondin exerts an inhibitory effect on the formation of cords in culture. These findings are in agreement with studies performed by other laboratories which suggest that thrombospondin is an anti-angiogenic protein. The ability of endothelial cells to invade, migrate, and proliferate into the connective tissue is in large part controlled by the immediate extracellular environment. We have provided evidence that endothelial cells can modify their microenvironment and secrete molecules that effect the morphogenesis of capillaries.